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13. ABSTRACT *(Maximum 200 words)*

This predoctoral fellowship has provided support for the training of Laurel Habel in the conduct of epidemiologic studies of breast cancer utilizing a variety of designs and analytic methods. Ms. Habel completed an analysis on the risk of contralateral breast cancer following breast cancer in situ (CIS). A cohort of 1929 women diagnosed with a first primary ductal or lobular carcinoma in situ between 1974 and 1993 in western Washington was followed for contralateral breast cancer through December 1993. After accounting for the estimated proportion of women treated with prophylactic mastectomy, rates of contralateral breast cancer were compared to population rates of first primary breast cancer using Poisson regression to adjust for age and calendar year. Rates of invasive cancer in the contralateral breast following CIS were two to three times higher than population rates and did not differ substantially by type of the initial CIS. Progress was also made on three other breast cancer projects. Other training during the fellowship period included participation in cancer reading and working groups and presentation of study results at a scientific meeting. During the fellowship period, Ms. Habel gained valuable skills and experience for a career in breast cancer epidemiology.

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Janet R Daling 7-14-95

PI - Signature Date

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Final Report

Predoctoral Fellowship in Breast Cancer

INTRODUCTION

The predoctoral fellowship provided support for the training of Laurel Habel in the field of breast cancer epidemiology. She is a doctoral student in the Department of Epidemiology at the University of Washington. Her primary research interests pertain to the biology and natural history of breast carcinoma *in situ*. Most of her research during the fellowship period involved examining factors related to the development of, or the risk of subsequent breast cancer among women diagnosed with, these tumors. Her research projects utilize three different study designs and analytic methods and have provided a broad range of training in epidemiologic methods. The University of Washington and the Fred Hutchinson Research Center are leading institutions in breast cancer research and Ms. Habel has had the opportunity to work with breast cancer researchers from a number of different disciplines.

I. Training

A. Research Projects in Breast Cancer Epidemiology

Research during the funding period included work on four breast cancer projects. Project 1, a study examining the risk of contralateral cancer following breast carcinoma in situ, was completed. Project 2 is the trainee's doctoral dissertation, and is not yet complete. This is a study designed to identify risk factors for recurrence following ductal carcinoma in situ. The majority of the trainee's time and energy was spent on this project. The first two projects required more time and effort than was anticipated at the time funding for predoctoral training was requested. Additional years of data were added for project 1, and the analysis was expanded. Although it was anticipated that project 2 would be completed by the end of the funding period, low response rates and difficulty locating study subjects who had moved and/or changed their names resulted in the need to extend the data collection time period. Because of the necessity to spend additional time and effort on projects 1 and 2, only limited work was accomplished on projects 3 and 4. Further, the initial work done on the latter two projects indicated that results would not be very meaningful.

Project 1. Risk of contralateral breast cancer following breast carcinoma in situ.

Introduction

The reported incidence of ductal (DCIS) and lobular (LCIS) carcinoma *in situ* of the breast has risen substantially during the last decade, due primarily to the widespread use of mammographic screening and to the greater tendency to biopsy suspicious lesions (Frykberg, 1991). It is not clear whether women diagnosed with an initial CIS have an elevated risk of subsequent contralateral breast cancer that is characteristic of women diagnosed with invasive disease (Donovan,1991; Horn-Ross,1993). Information is also limited on whether risk of contralateral invasive cancer differs by type of initial CIS.

The authors used data from a population-based cancer registry to evaluate whether women diagnosed with DCIS or LCIS are at greater risk of subsequent contralateral breast cancer than would be expected based on the rate of first primary breast cancer in the population. An additional aim was to compare the risk of subsequent invasive contralateral disease in women diagnosed with DCIS and LCIS.

Body

Methods

Women with CIS were identified through the Cancer Surveillance System (CSS). This population-based cancer registry serves 13 counties of western Washington and is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Cases included all women aged 20-84 years diagnosed with a first primary DCIS or LCIS between 1974 and 1993 who were residents of the 13 counties included in the registry catchment area at the time of diagnosis. Diagnoses of CIS were restricted to those confirmed by pathology and those that were either pure DCIS or pure LCIS. (3.8% of CIS diagnoses had ductal and lobular components and were excluded). LCIS included those tumors with the International Classification of Disease (ICD) code 8520; mixed ductal and lobular CIS were those tumors with ICD code 8522. All other ICD codes for carcinoma *in situ* of the breast were considered to be DCIS (Page,1991). Contralateral invasive cancers had the following ICD codes: 8211, 8401, 8500, 8501, 8520, 8522, and 8543. We categorized contralateral invasive cancers with ICD code 8520 as lobular, and those with ICD code 8522 as mixed ductal and lobular. All other invasive carcinomas of the breast were considered to be ductal. Women with a history of prior breast cancer were excluded. Also excluded were women whose contralateral cancer diagnosis occurred during the same month and year as the primary CIS diagnosis.

The cancer registry collects information on personal identifiers (name, social security number, date of birth, reporting institution) and assigns each individual diagnosed with cancer an identification number and each diagnosis of primary cancer a sequence number. Follow-up information (survival and diagnosis of subsequent primary cancer) on individuals diagnosed with cancer is ascertained annually by the CSS through a variety of data sources including hospital cancer registries and discharge data sets, the Department of Motor Vehicles registration files, the Health Care Financing Administration, and the Washington State death records. The length of follow-up for cohort members was measured as the time from diagnosis of the initial CIS to contralateral cancer, death, the last date the patient was recorded as residing in the CSS registry, or the end of the study period (December, 1993), whichever occurred first.

Although medical record abstraction by the CSS routinely includes information on the initial treatment regimen (treatment within, or documented as planned within, 4 months after initiation of treatment) for all patients with primary breast cancer, the computerized database does not contain information on treatment of the uninvolved breast. To estimate the proportion of women whose initial CIS treatment included prophylactic mastectomy of the contralateral breast, the cancer registry medical record abstract form was reviewed on a random sample of 50 women diagnosed with DCIS and 50 women diagnosed with LCIS who did not have subsequent contralateral cancer diagnosed. Based on our estimates of the proportion of women not treated with prophylactic mastectomy, 92% of women with DCIS and 76% of women with LCIS who were not subsequently diagnosed with contralateral cancer were randomly selected from the entire cohort and, along with all women diagnosed with contralateral disease, included in our analyses. Analyses included a total of 1929 women diagnosed with DCIS and 282 women diagnosed with LCIS.

SAS software (Statistical Analysis System) was used to stratify women with contralateral cancers and time at risk into 6 age groups (20-34, 34-44, 45-54, 55-64, 65-74, and 75-84) and 5 calendar year groups (1974-1977, 1978-1981, 1982-1985, 1986-1989, 1990-1993) (Pearce,1987). Rates of contralateral breast cancer were calculated and compared with population rates of first

primary breast cancer in western Washington using Poisson regression to adjust for age and calendar year (Breslow,1987). Population rates were based on data from the CSS. Rates of contralateral *in situ* and invasive disease for three time intervals (< 1 year, 1-4 years, and 5+ years) following the initial CIS diagnosis were compared with the population rate. Rates of contralateral *in situ* and invasive disease were also compared with population rates for different histologic types of breast cancer (ductal, lobular, and mixed ductal and lobular) for all time intervals combined. To minimize the potential bias resulting from increased medical surveillance of women diagnosed with CIS (Horn,1987; Neugut,1991), these same comparisons by histologic type of breast cancer were made after restricting cohort rates to the period 1+ years following diagnosis. The Kaplan-Meier model was used to estimate the percentage of surviving women who were free of cancer (either *in situ* or invasive cancer) in the contralateral breast at 5 and 10 years following diagnosis (Kahn,1989). Follow-up time of women was censored at the time of death, lost-to-follow-up, or end of the study period.

Results

The number of women diagnosed with either DCIS or LCIS rose substantially after 1985 (Table 1). Women with DCIS were slightly older at diagnosis than women with LCIS. Women with an initial DCIS were followed for an average of 56 months; 181 women were followed for at least 10 years. Women with an initial LCIS were followed for an average of 65 months; 39 women were followed for at least 10 years.

Table 1. Characteristics of Women Diagnosed with DCIS and LCIS

	DCIS (N=1929)		LCIS (N=282)	
	N	%	N	%
Age				
20-29	11	0.6	2	0.7
30-39	129	6.7	15	5.3
40-49	431	22.3	106	37.6
50-59	459	23.8	79	28.0
60-69	475	24.6	55	19.5
70-79	357	18.5	22	7.8
80-84	67	3.5	3	1.1
Diagnosis Year				
1974-77	112	5.8	27	9.6
1978-81	115	6.0	16	5.7
1982-85	249	12.9	54	19.1
1986-89	662	34.3	113	40.1
1990-93	791	41.0	72	25.5

A total of 80 (4.1%) women with DCIS had cancer diagnosed in the contralateral breast, of which 53 were invasive cancer. Based on the summary staging system used by SEER, 41 of the contralateral invasive cancers were local and 12 were regional stage at diagnosis. Cancer was

diagnosed in the contralateral breast of 41 (14.5%) women with LCIS. Of the 13 invasive cancers, 10 were local and 3 were regional stage at diagnosis.

Rates were extremely elevated for contralateral CIS during the year following diagnosis (Table 2). Among women with an initial DCIS, the rate of contralateral CIS was approximately 27 times the population rate; among women with LCIS, the rate was approximately 300 times the rate in the population. Rates of contralateral CIS remained elevated, but substantially less so, for the period 1-4 years following diagnosis for women with either DCIS or LCIS, and for the period 5 or more years after diagnosis for women with DCIS. There were no contralateral *in situ* cancers diagnosed among women with LCIS 5 or more years after diagnosis (expected based on population rate=0.08).

Rates of contralateral invasive cancer among women with an initial DCIS were approximately 1 1/2 to 2 times population rates and rate ratios (RR) did not appear to decrease with time since diagnosis. Among women with an initial LCIS, rates of contralateral invasive cancer were slightly higher than for women with DCIS and decreased somewhat with increasing time since diagnosis. Among women with an initial DCIS, the proportion without a subsequent cancer in the contralateral breast was 96.1% (95% CI=94.9%-97.0%) at 5 years and 91.6% (95% CI= 88.9%-93.6%) at 10 years. The proportion of women with LCIS without a subsequent cancer diagnosed in the contralateral breast was 84.8% (95 CI=83.7%-91.2%) at 5 years and 79.9% (95% CI= 72.3%-85.6%) at 10 years.

Table 2. Estimated Rate Ratios of Contralateral Cancer for Different Time Periods Following Diagnosis

	Contralateral Cancer					
	In situ Cancer			Invasive Cancer		
	N	RR*	95% CI	N	RR**	95% CI
Initial DCIS	**27**	**8.2**	**5.5-12.1**	**53**	**1.8**	**1.4-2.4**
Time since diagnosis						
< 1 year	16	27.6	16.9-45.1	10	1.9	1.0-3.6
1-4 years	7	4.4	2.1-9.2	22	1.5	1.0-2.4
5 + years	4	3.7	1.4-9.9	21	2.1	1.4-3.3
Initial LCIS	**28**	**53.5**	**36.3-79.3**	**13**	**3.0**	**1.7-5.1**
Time since diagnosis						
< 1 year	23	306.1	203.0-461.6	3	4.7	1.6-14.2
1-4 years	5	20.9	8.7-50.2	7	3.7	1.8-7.7
5 + years	0	0	0-45.3	3	1.7	0.5-5.1

*RR's are the ratios of the rate of *in situ* contralateral cancer among women in the study cohort to the rate of first primary *in situ* breast cancer in the population.

**RR's are the ratios of the rate of invasive contralateral cancer among women in the study cohort to the rate of first primary invasive breast cancer in the population.

RR's are adjusted for age (20-34, 35-44, 45-54, 55-64, 65-74, 75-84) and calendar year during which follow-up time accrued (1974-77, 1978-81, 1982-85, 1986-89, 1990-93).

***Exact confidence intervals for RR=0 were computed using equations for interval estimations for standardized mortality ratios (Breslow,1987).

The majority of contralateral *in situ* cancers following LCIS were also LCIS (20 of 28), and 82% were diagnosed within a year of the initial LCIS. Of the 27 contralateral *in situ* cancers following DCIS, 20 were also of ductal histology and 60% were diagnosed less than one year after the initial DCIS. Consequently, RRs of contralateral CIS by histologic type, especially among women with LCIS, were generally substantially higher when the time interval of <1 year following diagnosis was included in the estimate. (For example, the RR for DCIS following DCIS was 6.7 for all time intervals combined and 4.0 for the time interval 1+ years following diagnosis. The RR for LCIS following LCIS was 211.2 for all time intervals combined and 30.0 for the time interval 1+ years following diagnosis). The estimated RRs of metachronous disease (defined as 1+ years following diagnosis) by histologic type of the initial and contralateral cancer are presented in Table 3. The majority of all contralateral invasive cancers were ductal among women with either an initial DCIS or an initial LCIS (46 of 53 and 10 of 13, respectively). The same was true for metachronous disease. The rate ratio for metachronous mixed ductal and lobular invasive contralateral cancer was higher than that for invasive ductal cancer for women with either an initial DCIS or LCIS, although the number of these mixed histology cancers was quite small and the estimates imprecise.

Table 3. Estimated Rate Ratios of Metachronous* Contralateral Cancer for Different Histologic Types

	Contralateral Cancer					
	In situ Cancer			Invasive Cancer		
	N	RR*	95% CI	N	RR**	95% CI
Initial DCIS	**11**	**4.1**	**2.3-7.4**	**43**	**1.8**	**1.3-2.4**
Histology of contralateral cancer						
Ductal	9	4.0	2.1-7.6	37	1.7	1.3-2.4
Lobular	1	3.1	0.4-4.9	3	1.7	0.6-5.4
Mixed ductal and lobular	1	10.1	1.4-72.4	3	3.2	1.0-10.0
Initial LCIS	**5**	**11.1**	**4.6-26.6**	**10**	**2.7**	**1.5-5.0**
Histology of contralateral cancer						
Ductal	0	0	0-25.3	9	2.7	1.4-5.3
Lobular	2	30.9	7.7-124.1	0	0	0-29.8
Mixed ductal and lobular	3	159.8	50.4-506.6	1	6.7	1.0-46.9

*Contralateral disease 1+ years following initial CIS diagnosis.

*RR's are the ratios of the rate of the specific histologic type of contralateral CIS among women in the study cohort to the rate of first primary CIS of the same histologic type in the population.

**RR's are the ratios of the rate of the specific histologic type of contralateral invasive cancer among women in the study cohort to the rate of first primary invasive breast cancer of the same histologic type in the population.

RR's are adjusted for age (20-34, 35-44, 45-54, 55-64, 65-74, 75-84) and calendar year during which follow-up time accrued (1974-77, 1978-81, 1982-85, 1986-89, 1990-93).

***Exact confidence intervals for RR=0 were computed using equations for interval estimations for standardized mortality ratios (Breslow,1987).

Discussion

Our study has some limitations that should be considered when interpreting the results. Although we had a large cohort of women with CIS, the majority of women were diagnosed after 1985 and relatively few women were followed for more than 10 years. As with other cancer registry-based studies, histologic diagnoses of breast cancer were made by community pathologists and some misclassification of histologic types is likely to have occurred. Further, some women may have remained in the catchment area of the cancer registry past their last follow-up date but could not be located by CSS methods. The resulting underestimate of person-time is likely to be small, as approximately 94% of the cohort had positive evidence of residency within 12 months of the end of the study period, were known to have died, or were known to have developed contralateral breast cancer. An underestimate of person-time among the study cohort would have increased our RR estimates.

A review of the medical record abstract forms of a random sample of women in our study indicated that a substantial proportion of women diagnosed with LCIS and, to a much lesser extent, DCIS had been treated with a prophylactic mastectomy of the contralateral breast. Our estimates would be too low if some women had a prophylactic mastectomy that was not recorded by the CSS. The proportion treated by prophylactic mastectomy in our sample may have differed slightly from the proportion in the entire cohort and, because we assumed that these proportions were constant across age and calendar year, a small amount of confounding due to these factors may have been introduced if this was not the case. In an analysis that did not account for prophylactic mastectomy, the RR estimates were slightly lower than those presented in Table 2 (overall RR following DCIS was 1.7 versus 1.8, overall RR following LCIS was 2.4 versus 3.0).

Potential differences in screening patterns between the study cohort and the general population may affect our results. Women diagnosed with CIS in one breast are likely to have their uninvolved breast examined carefully for cancer. Women who were diagnosed with CIS with concurrent disease (diagnosis during the same month and year) in the contralateral breast were excluded from our study cohort, whereas women in whom no cancer was detected in the contralateral breast at the time of their initial diagnosis were included. Therefore, our cohort is likely to include a higher proportion of women with screened and clinically "healthy" breasts than the less intensively screened general population, to whom they were compared. This would result in rates in the study cohort being artificially low relative to population rates. However, intensive screening following a diagnosis of CIS could result in women being diagnosed with contralateral cancers early at the stage of CIS rather than at an invasive stage. This would artificially increase rates of contralateral CIS, and decrease rates of contralateral invasive disease, relative to population rates. Further, thorough and frequent screening or blind biopsy (without clinical evidence of disease) of the contralateral breast following a diagnosis of CIS could result in detection of cancers (especially CIS) that would not otherwise become clinically relevant disease.

The potential effect of screening differences is likely to be greatest immediately following a diagnosis of CIS. Rate ratios for contralateral CIS were quite elevated during the year following a diagnosis of either LCIS or DCIS, and then dropped dramatically, which is compatible with the occurrence of some detection bias. This pattern was not observed for contralateral invasive disease following DCIS; rates of contralateral invasive disease following LCIS decreased somewhat with time.

Women with a history of breast cancer (invasive or invasive and *in situ* disease combined) have an estimated risk of contralateral breast cancer that is 2-5 times the risk of first primary breast cancer (Horn-Ross,1993). Among women with an initial breast cancer, a family history of breast cancer, a young age at diagnosis of initial breast cancer, and a tumor of lobular histology (either invasive or *in situ*) have been found to be associated with increased risk of contralateral breast cancer (Donovan,1991, Horn-Ross,1993).

DCIS currently accounts for approximately 10-15% of all breast cancer diagnoses in western Washington. DCIS has been defined as the proliferation of malignant cells contained within the basement membrane of the mammary ducts without evidence of invasion (Breslow,1980). It is considered a non-obligatory pre-invasive lesion, as it appears as if some, but not all, DCIS will progress to invasive disease (Page,1991).

Most of the follow-up studies of women with DCIS have been small and few have reported on the incidence of contralateral breast cancer. Studies have differed with respect to several factors including patient selection criteria, procedures for examining the uninvolved breast, inclusion of synchronous contralateral cancers, length of follow-up, and whether only invasive contralateral cancers are considered as events. Three studies reported a five-year cumulative incidence of subsequent contralateral (*in situ* or invasive) cancer following DCIS of approximately 3-4% (Frazier,1977; Solin,1991; Fisher,1993). A lower incidence was reported by Webber et al. (Webber,1981). Among 116 patients with an initial DCIS, 3.4 % had contralateral breast cancer (either *in situ* or invasive) diagnosed during an average follow-up period of nine years (Webber,1981). Approximately 4.1% of women in our study with an initial DCIS were subsequently diagnosed with cancer in the contralateral breast during an average follow-up time of 54 months. One of the above studies also compared rates of contralateral cancer among women with DCIS to rates in the general population. After adjusting for age, race and calendar year, Webber et al. estimated a rate of contralateral that was approximately twice the population rate (Webber,1981). This relative rate estimate is lower than ours, but it was based on only 4 cases of contralateral disease (2 were invasive, 2 were *in situ*).

LCIS currently accounts for less than 3% of breast cancer diagnoses in western Washington. Unlike DCIS, LCIS is not seen on mammograms and is only detected microscopically (Page,1991). LCIS is defined as the presence of a monotonous proliferation within the lobule and terminal ducts of a characteristic pattern (Page,1991, Frykberg,1987). It is not clear whether LCIS is a preinvasive disease or rather a marker of increased risk for subsequent invasive breast cancer. Subsequent invasive cancers have been reported to occur with equal frequency in the ipsilateral and contralateral breast of women with LCIS and are commonly of ductal histology (Frykberg, 1991). Some pathologists now prefer to use the term lobular neoplasia for these lesions.

Much of the data available on contralateral breast cancer among women with LCIS also come from small studies and comparisons are difficult due to the same differences as listed for studies of DCIS. Approximately one third to one half of the women with LCIS who have had tissue from both breasts examined have been found to have bilateral LCIS (Rosen,1984). Four studies of women with LCIS with relatively long average follow-up time (each study had an average of over 15 years of follow-up) reported cumulative frequencies of contralateral invasive cancer of around 15% (Andersen, 1977;Haagensen,1978; Rosen,1978;Wheeler,1974). This is roughly compatible with our cumulative frequency of 4.6% for contralateral invasive disease following LCIS over an average follow-up time of 5.4 years.

Our RR estimate of 3.0 for contralateral invasive cancer following LCIS was based on relatively small numbers. The estimate is consistent with the findings of two other studies (Webber,1981; Rosen,1984), both of which also had few women with contralateral cancers and imprecise estimates. Rosen et al. followed a cohort of 175 women with LCIS (Rosen,1984), of which 26 were diagnosed with contralateral cancer (invasive and DCIS, combined). Age and calendar-year adjusted rates of contralateral cancer were approximately 5-10 times those expected based on the rate in the population. Rates were based on breast-years at risk, providing estimates that are double those based on person-years at risk (our analysis). Webber et al. followed 68 women with LCIS. The age, race and calendar-year adjusted rate of contralateral cancer (based on person-years) was approximately seven times the rate in the population; 4 of the 7 contralateral cancers were *in situ* (Webber,1981).

In our study population, almost 50% of all contralateral cancers following LCIS were also LCIS. The very high relative rate of contralateral CIS during the first year following diagnosis of the initial LCIS appears to have been influenced by the practice of blind biopsy or prophylactic mastectomy (and pathologic examination) of the contralateral breast. Limited information obtained from a review of CSS medical record abstract forms suggested that as many as 60% of contralateral cancers found within the first year following an initial diagnosis of LCIS were identified because of a prophylactic mastectomy or blind biopsy of the contralateral breast. Contralateral breast cancer following invasive lobular carcinoma has also been reported to be particularly elevated during the first year following diagnosis (Horn-Ross,1993). It is possible that this finding is due in part to more intensive examination of and tendency to biopsy the contralateral breast of women with invasive lobular cancer (Horn,1987; Hislop,1984) .

Given that LCIS is more often bilateral than DCIS and it is thought to be either a marker for high risk breast tissue or a pre-invasive lesion, it is surprising that the contralateral breast of women with an initial LCIS is not at substantially greater risk of subsequent invasive cancer than the contralateral breast of women with an initial DCIS. It is conceivable that our rate ratio estimates would change if we could follow large numbers of women with LCIS for a longer period of time. High risk breast tissue identified by LCIS lesions may progress very slowly towards invasive disease. In one study, over a third of the contralateral cancers following a diagnosis of LCIS occurred more than 20 years following diagnosis (Rosen,1981).

Conclusions

In summary, our data suggest that the risk of contralateral breast cancer is elevated for at least 5 years following a diagnosis of CIS compared to the risk of first primary breast cancer in the population. Rates of contralateral CIS are substantially higher for women with LCIS than for women with DCIS, but this is due in large part to contralateral LCIS diagnosed during the first year following the initial LCIS. Although LCIS has been considered a risk factor for bilateral breast cancer, the rates of contralateral invasive cancer appear to be only slightly higher for women with an initial LCIS than for women with an initial DCIS. The elevated rate of contralateral invasive disease following CIS appears to be similar to that reported for women with invasive breast cancer. Increase medical surveillance is likely to be partially responsible for the markedly elevated rates of contralateral CIS diagnosed during the first year following a diagnosis of CIS, and to the extent that this increased surveillance continues, for any subsequent time period. It is possible that increased medical surveillance of women with CIS also influences the subsequent rates of contralateral invasive breast cancer. Future studies of bilateral breast

cancer should consider obtaining detailed information on breast cancer screening, biopsy and prophylactic mastectomy in order to better understand the potential influence of increased medical surveillance on the diagnosis of contralateral breast cancer among women with either *in situ* or invasive disease.

Project 1 status: This project has been completed. During the funding period, the cancer registry data for this project was updated with two additional years of cases and the analysis was redone and expanded. The manuscript was prepared and has been submitted for publication.

Project 2. Risk of recurrence (ipsilateral or metastatic disease) among women diagnosed with ductal carcinoma in situ (DCIS) and treated with breast-conserving therapy. This is the trainee's doctoral dissertation.

Introduction

There has been a dramatic increase in the diagnosis of DCIS during the last 5-10 years, mainly due to the increase use of and improvement in mammographic screening procedures (Frykberg,1991). DCIS currently accounts for as many as 15-20% of breast cancers diagnosed in screened populations (Baker, 1982;Verbeek,1984). Much remains unknown about the biology and natural history of these lesions and factors have not been identified that can accurately predict which DCIS tumors will locally recur or progress to invasive disease.

This study uses a population-based case-cohort design (Wacholder, 1991) to identify patient and tumor characteristics associated with breast cancer recurrence among a cohort of women diagnosed with DCIS and treated with breast-conserving therapy.

Body

Methods

Cohort Identification: The cohort was comprised of women diagnosed with a first primary DCIS between January 1980 and June 1992 who were treated with breast-conserving therapy. Study subjects were identified through the Cancer Surveillance System, a population-based tumor registry operating in western Washington as part of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Women were excluded if they were not residents of the 13-county area covered by the registry at the time of initial diagnosis with DCIS, if treatment for their initial DCIS included mastectomy, or if they reported a prior breast cancer.

Data Collection: Study subjects were sent a structured self-administered questionnaire to obtain information on the occurrence of subsequent breast cancer or metastatic disease and to collect information on individual characteristics and exposures. Approximately 30% of subjects preferred to provide the information during a telephone interview conducted using the same questionnaire. A random sample of the 35% of the cohort (subcohort) was selected for tissue slide and block retrieval for assessment by a pathologist. Tumor tissue will be assessed for several histopathologic features, including histologic subtype, nuclear grade, and the presence of necrosis.

Statistical Analysis: Kaplan-Meier modeling will be used to calculate cumulative incidence rates of recurrence. Cox proportional hazards modeling will be used to estimate the relative risks and 95% confidence intervals, with the variance adjusted for the influence of cohort sampling.

Preliminary results

Characteristics of the Study Cohort

Characteristic	No Recurrence N	%	Recurrence N	%
Year of DCIS diagnosis				
1980-83	17	3.7	8	10.3
1984-87	126	27.5	30	38.5
1988-92	316	68.8	40	51.3
Age at DCIS diagnosis				
20-29	5	1.1	0	0
30-39	25	5.4	5	6.4
40-49	121	26.4	22	28.2
50-59	129	28.1	21	26.9
60-69	132	28.8	24	30.8
70-74	47	10.2	6	7.7
Race				
White	422	91.9	72	92.3
Black	5	1.1	1	1.3
Asian	32	7.0	4	5.1
Unknown	0	0	1	1.3
Marital Status at Diagnosis				
Single	24	5.2	8	10.3
Married	322	70.2	51	65.4
Widowed/Divorced/Separated	89	19.4	13	16.7
Unknown	24	5.2	6	7.7
Histology of DCIS				
Comedo	99	21.6	17	21.8
Noncomedo/not specified	347	75.6	58	74.4
DCIS with LCIS	13	2.8	2	2.6
Unknown	0	0	1	1.3
Treatment with Radiotherapy				
No	209	45.5	46	59.0
Yes	250	54.5	31	39.7
Unknown	0	0	1	1.3

* Data on subject characteristics were obtained from information collected by the CSS. Information on recurrences was obtained from the study subject, cancer registry records (1991-1995), or the subject's follow-up physician.

Project 2 Status: This study is still in progress. As noted in Section I.A, low response rates and difficulty locating study subjects who had moved and/or changed their names resulted in the need to extend the data collection time period. During the study period, approximately 80 active physicians were located and sent letters requesting consent to contact patients. Letters of contact

and questionnaires were sent to over 200 study subjects. Approximately 50% of these women needed telephone reminders to return the questionnaire. The questionnaires were edited, data entry programs were developed, and data entry was initiated. The collection of data from study subjects is now complete. Tumor tissue has been requested on approximately 150 subjects. Retrieval of tissue slides and blocks for pathology review will continue through the end of 1995. Data editing and entry are continuing and should be completed by February, 1996. The study analysis and manuscript preparation is anticipated to be completed during 1996.

Project 3. Risk factors for *in situ* and invasive breast cancer in women aged 50-64.

Introduction

Although DCIS is considered a precursor lesion of invasive breast cancer, few studies have examined risk factors for DCIS to determine if they are similar to factors that have been found to be associated with risk of invasive disease. This analysis uses data from a case-control study designed primarily to evaluate the relation between hormone replacement therapy and breast cancer risk to examine established and suspected risk factors for breast cancer with emphasis on factors found or hypothesized to promote tumor development or progression, such as obesity (Verreault,1989).

Body

Methods

Cases were identified through the Cancer Surveillance System. This population-based cancer registry serves 13 counties of western Washington state and is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Eligible cases included all white women aged 50-64 years who were diagnosed with histologically confirmed first primary invasive or *in situ* carcinoma of the breast between January 1988 and June 1990 and who were residents of King County, Washington at the time of diagnosis. A total of 660 eligible cases were identified, of whom 537 (81.4%) were interviewed. Reasons for non-response included refusals (12.6%), location problems (1.5%), communication problems (0.6%), and death (3.9%).

Controls were selected by randomly dialing telephone numbers in King County using the method described by Waksberg. In order to minimize geographic clustering of controls that can occur using the Waksberg-Mitofsky Method of random digit dialing, we used a clustering factor of two residences per sampling unit (denoted "k" by Waksberg). One step recruitment was used with a stratified sampling design that recruited controls into age strata (50-54, 55-59, 60-64) throughout the control ascertainment period· Controls were randomly assigned a reference date (month and year) that approximated the distribution of diagnosis dates among the cases. Complete household census information was obtained for 96% of the residences contacted. We identified 747 eligible women based on household screening and completed interviews on 545 (73.0%). Fifty-three women who reported a previous diagnosis of breast cancer or who were non-white were excluded, leaving 492 controls for analysis.

Information was obtained from study subjects during an in-person interview using a structured questionnaire that pertained to events prior to diagnosis date (cases) or reference date (controls). The interview included questions regarding established and suspected risk factors for breast cancer such as menstrual and reproductive histories, use of exogenous hormones, family

history of breast cancer, body size indicators, diet and alcohol consumption, smoking habits, and social and demographic factors.

Logistic regression was used to estimate relative risks and 95% confidence intervals, while controlling for the confounding effects of other variables.

Preliminary Results

Table 1. Characteristics of Cases and Controls

Characteristic	Control (N=492)	Invasive (N=450)	In situ (N=87)
Age, y			
50-54	152	123	29
55-59	171	164	29
60-64	169	163	29
Number of full-term pregnancies			
0	46	56	9
1-2	171	158	33
3+	275	236	45
Age at first full-term pregnancy			
15-19	103	70	12
20-29	318	296	57
30+	25	28	9
Nulliparous	46	56	9
Family history			
None	182	149	36
First degree	66	75	15
Second degree	54	76	14
Unknown	190	150	22
Body mass index, kg/m^2			
<21.1	123	92	21
21.2-23.6	123	108	24
23.7-27.1	122	124	18
≥27.2	123	126	24
Alcohol use, drinks per week			
Never	96	58	16
<1	122	132	25
1-3	132	127	21
4-6	69	63	10
7+	70	70	15

Table 2. Relative risks associated with selected characteristics

	Invasive Cancer		In situ Cancer	
Characteristic	**RR***	**95 % CI**	**RR***	**95% CI**
Number of full-term pregnancies				
0	1.0	reference	1.0	reference
1-2	0.7	0.5-1.1	1.0	0.4-2.2
3+	0.7	0.4-1.0	0.8	0.4-1.8
Age at first full-term pregnancy				
15-19	0.5	0.3-0.9	0.6	0.2-1.4
20-29	0.7	0.5-1.1	0.9	0.4-1.9
30+	0.9	0.5-1.7	1.9	0.6-5.5
Nulliparous	1.0	reference	1.0	reference
Family history**				
None	1.0	reference	1.0	reference
First degree	1.4	1.0-2.1	1.3	0.7-5.5
Second degree	1.7	1.1-2.6	1.3	0.7-2.6
Unknown	1.0	0.7-1.3	0.7	0.4-2.7
Body mass index**				
<21.1	1.0	reference	1.0	reference
21.2-23.6	1.2	0.8-1.7	1.2	0.6-2.3
23.7-27.1	1.4	1.0-2.0	0.9	0.4-1.7
≥27.2	1.5	1.0-2.1	1.2	0.6-2.3
Alcohol use, drinks per week**				
Never	1.0	reference	1.0	reference
<1	1.7	1.2-2.6	1.1	0.6-2.3
1-3	1.6	1.0-2.3	0.9	0.4-1.8
4-6	1.5	0.9-2.4	0.8	0.3-1.9
7+	1.6	1.0-2.6	1.2	0.5-2.6

*RR's adjusted for age, family history of breast cancer, and number of mammograms prior to reference date.
**RR's also adjusted for age at first full-term pregnancy.

Project 3 status: Preliminary analysis performed during the funding period suggested that risk factors are similar for *in situ* and invasive breast cancer. Unfortunately, as the number of *in situ* cases is small and the differences for invasive and *in situ* disease modest, this study does not appear to have the power to evaluate whether observed differences (or similarities) are real or the result of chance alone. Further analyses are unlikely to provide meaningful information and no additional work is planned for this project.

Project 4. Occupational exposures and breast cancer risk. Prior to the initiation of predoctoral funding, a paper that was presented by the trainee at NCI's Conference of Women's Health:

Occupation and Cancer in November, 1993 on the association between occupation and breast cancer risk in middle-aged women was submitted for publication. During the training period, effort was made to examine the association between occupational exposure to electromagnetic fields (EMFs) and breast cancer risk in this same study population of women aged 50-64. Study subjects were categorized into levels of potential EMF exposure based on an exposure algorithm developed to classify men's occupational histories (Demers, 1991). Using this exposure algorithm, only approximately 2% (N=21) of the 1029 study subjects reported spending time in occupations with potential exposure to high levels of EMF. Given the study size, this exposure prevalence was too small to provide meaningful information about the association of occupational EMF exposure and breast cancer risk in middle-aged women. No further work is planned for this project.

B. Memberships in Cancer Reading and Working Groups

Cell Biology and Cancer Reading Group, Fred Hutchinson Cancer Research Center, March 1995 - present.

Clinical Breast Cancer Working Group, University of Washington, September 1994 - present.

C. Symposiums and Scientific Meetings attended

49th Annual Cancer Symposium for the Society for Surgical Oncology, Boston, March, 1995.

Screening for Genetically Susceptible Women and for Early Breast Cancer. Seattle Breast Cancer Research Program Retreat, June 1995

II. Bibliography

A. Publications

None to date as a result of contract support.

B. Meeting Abstracts

Habel LA, Daling JR, Moe RE. Risk of contralateral breast cancer following breast carcinoma in situ. 49th Annual Cancer Symposium for the Society for Surgical Oncology, Boston, March, 1995.

III. Personnel Receiving Pay

Laurel A. Habel, pre-doctoral training only. The initial proposal requested a stipend for Ms. Habel for 12 months. The amount requested was based on the University of Washington's set rate for a Research Assistant. Since the amount requested was cut by approximately 27%, the

funding could only cover the trainee for 9.5 months (see appendix for documentation). Although Ms. Habel only received funding from the U.S. Army Medical Research and Material Command for a period of 9.5 months, her work continued throughout the 12 month period, during which time her salary came from another source. She continues to work on her dissertation project.

IV. Graduate Degrees Received

None; Ms. Habel hopes to finish her doctorate by June, 1996.

CONCLUSIONS

This predoctoral fellowship has provided support for training of Laurel Habel in the conduct of epidemiologic studies of breast cancer using a variety of designs and analytic methods. Ms. Habel completed an analysis and manuscript on the risk of contralateral breast cancer following breast carcinoma in situ. Progress was also made on three other breast cancer research projects. Although it was anticipated that a study on the risk of recurrence following DCIS would be completed by the end of the funding period, low response rates and difficulty locating study subjects who had moved and/or changed their names resulted in the need to extend the data collection time period. Only limited work was accomplished on projects 3 and 4, due in part to the necessity to spend additional time and effort on the first two projects and because the initial work suggested that study results would not be meaningful. Other training during the fellowship period included participation in cancer reading and working groups and presentation of study results at a scientific meeting. She has gained valuable experience and skills necessary to pursue research in breast cancer, including research in the biology and natural history of pre-invasive breast tumors.

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APPENDIX

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
FORT DETRICK, FREDERICK, MD 21702-5014

REPLY TO ATTENTION OF:

JUL 20 1994

General Research Contracts Branch

DADMD17-94-J-4148

SUBJECT: Breast Cancer Proposal entitled "Risk of Recurrence Following Breast-conserving Therapy for Ductal Carcinoma" under the direction of Dr. Janet Daling

Mr. Paul Pearson
University of Washington
Grants and Contract Services
Seattle, Washington 98195

Dear Mr. Pearson:

Please refer to Dr. Janet Daling's proposal and budget dated 10 November 1993, submitted in response to the U.S. Army Breast Cancer Broad Agency Announcement for training support in the amount of $27,433.

As we had discussed in June, the BCBAA requirement for Training and Recruitment set some restrictions on the amount of the awards The limits were set at up to $20,000 annually per trainee. Before I can go any further with discussions or considerations, I will need a revised budget to comply with the cap.

Please notify us of your intentions by 25 July 1994, allowing our organization the opportunity to redistribute the funding. Since this was a certain type of money, it must be obligated by mid-September 1994, therefore, please expedite your response.

Sincerely,

Nancy G. Mohler
Contracts Specialist

Section I
DETAILED COST ESTIMATE
October 1, 1994 - September 30, 1995

Direct Labor Costs and Fringe Benefits

Name	Role on Project	% Time on Project	Months on Project	Base Salary	Salary Charged to Project	Fringe Benefits Rate	Fringe Charged to Project	Total
Laurel A. Habel	Predoctoral Research Associate	50%	12	$29,568	14,784	10%	1,478	$16,262

Materials, Supplies, and Consumables

General Office and Computer Supplies	$33

Other Direct Costs

Graduate Student Operating Fee (tuition): 3 quarters at $1,399 and 1 quarter at $948	$5,145
Photocopying and Postage	$67
	$21,507
Indirect Costs, 27.6% of Total Direct Costs	$5,936
Total	$27,443

Breast Cancer Proposal entitled "Risk of Recurrence
Following Breast-conserving Therapy for Ductal Carcinoma"
under the direction of Dr. Janet Daling

Section I
DETAILED COST ESTIMATE
October 1, 1994 - July 15, 1995

Direct Labor Costs and Fringe Benefits

Name	Role on Project	% Time on Project	Months on Project	Base Salary	Salary Charged to Project	Fringe Benefits Rate	Fringe Charged to Project	Total
Laurel A. Habel	Predoctoral Research Associate	50%	9.5	$22,078	$11,039	10%	$1,104	$12,143

Materials, Supplies, and Consumables

General Office and Computer Supplies	90

Other Direct Costs

Graduate Student Operating Fee (tuition): 3 quarters at $1,399	4,197
Photocopying and Postage	181
	$16,611

Indirect Costs, 27.3% **of Total Direct Costs** 3,389

Total $20,000

DADMD17-94-J-4148

UNIVERSITY OF WASHINGTON

PERSONNEL ACTION (PAF)

PAYROLL/PERSONNEL

SHADED AREAS FOR PAYROLL/PERSONNEL ONLY

IDENTIFICATION

Social Security Number	Name (Last, First (space) M.I.)	Name Suffix	Empl. Mail Stop	Employment Date	Date Prepared	Empl. Stat.	PAF Gen.
567-86-3122	[redacted]		BC-36	09 16 89	10 18 94	A	041
				MO DY YR	MO DY YR		

Personnel Actions (Check 1 to 3 Actions)

									Personnel Action Date	Prior Personnel Actions
☐ 01 Initial Emp.	☐ 05 Merit Increase	☐ 09 Change to % Full Time	☐ 14 Reassignment	☐ 18 Lv. Ab. W/O Pay	☐ 22 Demotion Discp.	☐ 30 Lateral Move	☐ 34 Appt Change	☐ 38 Competitive Offer	09 01 94	10
☐ 02 Separation	☐ 06 Gen. Salary Adjust.	☐ 10 Change to Distribution	☐ 15 Transfer	☐ 19 Rt. From Lv. Ab.	☐ 23 Discp. Suspension	☐ 31 Name Change	☐ 35 Rehire			
☐ 03 Promotion	☐ 07 Temp.Sal.Inc. (St./Stp.)	☐ 11 Reappointment	☐ 16 Job Reclass	☐ 20 Rehired Partial Emp.	☐ 24 Reverson	☐ 32 Title Change	☐ 36 Mass. Bud. No. Chg.			
☐ 04 Increment	☐ 08 Spec. Prem. Pay	☐ 12 Exten. of Appt. (Summer)	☐ 17 Lv. Ab. With Pay	☐ 21 Demotion Volun.	☐ 25 SS/ID Correction	☐ 33 Future Appt.	☐ 37 Auto. Sal. Inc.		MO DY YR	

Home Department			H/D Mail Stop	P/T	F/P	SVC. Period	Seprtn	Student ID Number	Lv. of Ab. Return Dt.	LvAbRea	Ext	Regents Approval Date	Tenr.	Tenure Date
[redacted]	808	DEPT OF EPIDEMIOLOGY	BC-36	T	P	12.0		0086936653						
Budget No.	Unit No.	Name							MO DY YR			MO DY YR		

APPOINTMENT

Appointing Department			Job Class	Appointment Title	Job Class Entry Date	Prob./Trial Period End Dt.	Incr. Mo
[redacted]	808	DEPT OF EPIDEMIOLOGY	[redacted]	[redacted] ASSOCIATE	09 01 94		
Budget No.	Unit No.	Name			MO DY YR	MO DY YR	

Appt. No.	Appointment Start Date	Appointment End Date	Appt. Term	Appt. Stat.	Range	Step	Full-Time Rate	M/H	Pay Cy.	Appt. % of FTE	Appointment Pay Rate	Work Cnty.	W/S	State W/S Amount	Federal W/S Amount
[redacted]	09 01 94	06 30 95	10.0	[redacted]						50.00	1,162.00				
	MO DY YR	MO DY YR													

DISTRIBUTION

Notes and Comments

Dist.	Distribution Start Date	Distribution End Date	P/C	Budget Number	Object Code	Cost Accounting			Position No./Sub.	Earn Type	Dist. % of FTE	Distribution Amount
1	09 01 94	06 30 95	100	[redacted]	[redacted]				0865	GSA	50.00	1,162.00
	MO DY YR	MO DY YR				Task	Optn.	Project				
2												
	MO DY YR	MO DY YR				Task	Optn.	Project				
3												
	MO DY YR	MO DY YR				Task	Optn.	Project				
4												
	MO DY YR	MO DY YR				Task	Optn.	Project				
5												
	MO DY YR	MO DY YR				Task	Optn.	Project				
6												
	MO DY YR	MO DY YR				Task	Optn.	Project				
7												
	MO DY YR	MO DY YR				Task	Optn.	Project				

DADMD17-94-J-4148

APPROVAL/AUTHORIZATION SIGNATURES

Home Department Signature	Date	Preparer Name	Campus Phone	College/Division Signature	Date	Personnel Signature	Date

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 21 Apr 97

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-OCP, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for Grant Number DAMD17-94-J-4148. Request the limited distribution statement for Accession Document Number ADB206807 be changed to "Approved for public release; distribution unlimited." This report should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322.

FOR THE COMMANDER:

for Pauline Rinehart
GARY R. GILBERT
Colonel, MS
Deputy Chief of Staff for
Information Management

Completed 1-10-00 ar